

Royal National Institute for the Blind

224 Great Portland Street, London W1N 6AA



RESEARCH WORK FOR THE PREVENTION OF BLINDNESS 1973 - 1979

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ROYAL NATIONAL INSTITUTE FOR THE BLIND

PREVENTION OF BLINDNESS

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died November 1978, replaced by
Dr. Donald M. Smith, November 1978,
Employment Medical Advisor

Department of Education and Science:

Dr. S. R. Fine (Medical Officer)
resigned November 1978, replaced by
Dr. Richard Burns (Medical Officer),
November 1978

INTRODUCTION

We are most grateful to Dr. Ruth van Heyningen for undertaking the preparation of this report. Dr. van Heyningen put much time and work into collating and summarising information sent to her in various forms from many sources.

This report brings up to date the account of RNIB sponsored research. Earlier reports cover 1962-1967 and 1967-1972.

Members of RNIB's Prevention of Blindness Sub-Committee are drawn from RNIB's Council, the Faculty of Ophthalmologists, the Association of Metropolitan Authorities, the Association of County Councils and the Departments of Health and Social Security, Employment and Education and Science.

During the period covered by this Report, grants of over £120,000 have been made to individuals and institutions carrying out research into the prevention of blindness.

Eric T. Boulter
Director General
Royal National Institute for the Blind

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BATH EYE INFIRMARY

T. Stuart-Black Kelly, FRCS

In 1976 Dr. T. Stuart-Black Kelly was granted £500 towards the expenses of a journey to Japan. For many years he has studied various methods which may be used in attempts to arrest the development of myopia in children and young people; myopia in the Japanese is more common and more severe than in the Caucasian. Dr. Kelly wished to observe the methods used by leading authorities in Japan for treating and arresting myopia and to see what changes in treatment had been made since his visit in 1968. He also wished to see if any of his ideas could be of value to the Japanese. On his return he wrote a detailed and informative report of his experiences and this should prove a useful basis for further work on this important and controversial topic.

BIRMINGHAM AND MIDLAND EYE HOSPITAL

Vernon H. Smith, FRCS, Consultant Ophthalmologist
J. S. Hillman, FRCS

In 1973 the RNIB assisted Mr. Vernon Smith and his colleagues to purchase a 'B' Scan Ophthalmic Bronson-Turner Ultrasonograph. This apparatus was to complement their existing 'A' Scan Ultrasonograph. The purpose of their planned research was to make a critical and painstaking assessment of the usefulness of the technique of ultrasonography to the ophthalmologist.

They found that, in the hands of a practised operator, the A-Scan ultrasonograph and the B-Scan ophthalmic Bronson-Turner ultrasonograph can be used to obtain considerable information in both intraocular and orbital conditions. They are excellent for detecting intraocular pathology provided that a methodical and comprehensible scan of the eye is made. Under these circumstances, it is possible to detect with ease whether the patient has a retinal detachment, whether this is full thickness retina or retinoschisis, and whether the detachment is solid. They will not, however, give any information as to the type of solid lesion.

They are perhaps less informative in mapping out areas of organised vitreous haemorrhage due to the reduced echo, and a delay tube is required to obtain accurate information on the anterior segment.

So far as the orbit is concerned, it is possible to detect space occupying lesions, but again, they give no information as to the nature of these lesions, except possibly with larger haemangiomas. It is possible to measure the thickness of the extraocular muscles in endocrine exophthalmos, but considerable experience is needed for this.

Finally, for any ocular measurement, these provide a rough guide of the length of the eye and the depth of the orbit, but the attenuation of the signal due to differing acoustic density, makes it impossible to regard these as strictly accurate.

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- Hillman, J. S. (1975) 'Retinoschisis and retinal detachment - an ultrasonic comparison' 'Ultrasonography in ophthalmology' Bibl. Ophthalmology No 83 63 - 67
- Hillman, J. S. (1973) 'Diagnostic ultrasonography in ophthalmology' British Journal of Hospital Medicine 10, 541 - 550
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CITY UNIVERSITY, LONDON

Professor Douglas Gordon, MB, DMR, DMRD, SMIEEE
Honorary Consultant Radiologist, Moorfields Eye Hospital
Visiting Professor of Bio-Medical Engineering, The City University, London

In 1975 Professor Gordon received a grant from the Royal National Institute for the Blind to assist him in the construction of an apparatus for use in the Doppler ultrasonic measurement of the circulation in the central retinal artery. Professor Gordon is an electrical engineer and a physicist as well as a radiologist and he has constructed the apparatus himself. The research project is progressing well.

The use of ultrasonic rays for medical diagnosis has become widely accepted since it was introduced twenty-five years ago using an echo system comparable to echo-sounding. For the last ten years it has been extended into the measurement of blood velocity by using the Doppler principle. At first it was used to measure the blood moving inside the heart and the large vessels but about eight years ago it was demonstrated at the High Holborn branch of Moorfields Eye Hospital that it was possible to obtain signals from the blood vessels that supply the eye and orbit.

The most important of these is the central retinal artery which travels within the substance of the optic nerve from the point at which it leaves the interior of the skull. When it reaches the eye it divides into branches which can be seen by the ophthalmologist. Within the eye the circulation can be studied by fluorescein photography but until now it has not been possible to detect disease in the main part of the artery where any blocking causes complete loss of vision in that eye.

The main ophthalmic artery can with difficulty be demonstrated by X-ray angiography but this is a major investigation with some hazard attached. It is quite impossible to detect, in this manner, an artery less than a millimetre in diameter. Ultrasound, however, produces signals which, though at the lower end of the audible range, can be analysed using techniques closer to those used by seismologists to study earthquakes than those used to study music.

The eye in the conscious patient cannot be immobilised and the small rotational movements of the eye produce artefacts that have proved difficult to distinguish from the significant signal. Conventional tape-recording has similarly proved quite inadequate so progress has been very slow. However, it has been shown beyond doubt that accurate quantitative measurements are possible and the development of an instrument capable of being used by a clinician without technical acoustic knowledge can be forecast with reasonable certainty.

MANCHESTER ROYAL EYE HOSPITAL

A. E. A. Ridgway, Consultant Ophthalmic Surgeon

A grant of £2,530 was made towards the purchase of an endothelial microscope and additional parts to make it easier to use. Owing to difficulties with the original manufacturers, who have now been taken over by another firm, the project has been delayed. However, Mr. Ridgway is now in the position to start to use the microscope to study the in vivo survival of corneal endothelium, to investigate grafted patients for hormonal or cell-mediated immune responses to donor lymphocytes, and also to investigate the survival of endothelium in grafted patients.

THE INSTITUTE OF OPHTHALMOLOGY
UNIVERSITY OF LONDON

IN ASSOCIATION WITH MOORFIELDS EYE HOSPITAL
DEPARTMENT OF EXPERIMENTAL OPHTHALMOLOGY

Director: Professor E. S. Perkins, MD, PhD, FRCS
R. A. F. Whitelocke, MB, FRCS
K. E. Eakins, B Pharm, PhD
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DEPARTMENT OF CLINICAL OPHTHALMOLOGY

John Thomsitt, FRCS
Janet Silver, FBOA, Principal Ophthalmic Optician
Elizabeth Gould, BSc, FBOA, Ophthalmic Optician

DEPARTMENT OF VISUAL SCIENCE

Director: Professor R. A. Weale, DSc, PhD
R. F. Fisher, BSc, PhD, MD, BS, FRCS

MOORFIELDS EYE HOSPITAL

Eva M. Kohner, MD, MRCP

Department of Experimental Ophthalmology

(1) The role of prostaglandins in ocular inflammation

Prostaglandins are known to be released into the aqueous of rabbit eyes following chemical irritation or trauma. Experimental uveitis was induced in rabbits by the intravitreal injection of bovine serum albumen which is followed in about ten days by a severe uveitis very similar to the acute human disease. Substantial amounts of a prostaglandin E₁-like substance were found in the aqueous of the experimental eyes. The biological assay and thin-layer chromatography on the samples were carried out in collaboration with Dr. A. Bennett at King's College Hospital Medical School. The origin of the prostaglandin in the aqueous is still not certain but the results suggest that it may be derived from leucocytes attracted to the eye by the antigen-antibody reaction taking place.

Samples of human aqueous from patients with active uveitis were studied. Substantial amounts of prostaglandin-like activity (20-56 ng/nl) were found in untreated cases. Little activity was found in the aqueous from patients who had received treatment with corticosteroids and none was found in aqueous from uninflamed eyes of patients with cataract. Alkaline hydrolysis of the samples from inflamed eyes suggested the presence of both E and F prostaglandins.

This is the first time that prostaglandins have been isolated from the tissues in a spontaneous human disease, and is an exciting indication that at least some of the ocular changes in uveitis are due to prostaglandins. It opens up new therapeutic possibilities for the use of prostaglandin antagonists.

Various antagonists are now being investigated using the technique of fluorescein iris angiography developed by Dr. Whitelocke. Two substances have so far been shown to inhibit the vasodilatation and increased vascular permeability normally produced by prostaglandins. The next step is to test these antagonists on experimentally induced uveitis and to compare their anti-inflammatory activity with that of corticosteroids and other anti-inflammatory agents.

(2) Fluorescein iris angiography in human eyes

The technique of simultaneous iris angiography developed by Dr. Whitelocke has enabled valid comparisons to be made of the blood flow in the iris of the two eyes. Unfortunately, it can only be used in eyes with a light coloured iris, which rather restricts its usefulness, but the vascular changes in conditions such as heterochromic uveitis can be clearly shown. The technique is also being used to disclose the earliest changes in the anterior segment in patients who have had a retinal vein thrombosis.

Publications:

Eakins, K.E., Whitelocke, R.A.F., Bennett, A. and Martenet, A.C. (1972) Prostaglandin like activity in ocular inflammation. Brit med J 3, 452.

Eakins, K.E. Whitelock, R. A. F., Perkins, E. S., Bennett, A. and Unger, W. G. (1972) Release of prostaglandins into the aqueous humour in experimental immunogenic uveitis. Nature, 239, 248.

Department of Clinical Ophthalmology

John Thomsitt, FRCS

Jan Carter, MSc, BA, Dip Soc Studies

A survey of Patterns of Eye Injuries in Children, made at Moorfields Eye Hospital, was supported by the RNIB. A study of 296 children's eye injuries showed that, whilst most accidents have no permanent consequences, specific age and sex groups in which most accidents occur could be defined. School boys of 9-10 years and 13-14 years had most ocular accidents and boys are much more likely than girls to have severe accidents with permanent visual defects. Cigarette burns are prominent in the pre-school group. This suggests that educational strategies can be specifically employed.

A detailed study of the interaction of the accident with background characteristics in three referred families indicated patterns concerned with family structure, housing, supervision and the pathway to medical care. Severe and repeated accidents were compared, and some suggestions for further work were made.

Messrs. Thomsitt and Carter have emphasised that eye injuries occur as a result of multifarious social processes and have discussed the possibilities of their prevention, against the background of the host-agent environmental relationships with specific target groups located for directing effort in the prevention of eye accidents. They have also discussed the organisation of services including health education, delivery of services and systems of recording.

Department of Visual Science

Dr. R. F. Fisher has made a detailed study of the mechanical properties of the human lens, using a micro-manipulator purchased in 1969 with the aid of a grant from the RNIB to Professor R. A. Weale. The results of one facet of this work led him to suggest that some of the senile variations found in the human lens may be related to a predisposition to senile cataract. The lens in vivo is subjected to mechanical stresses during the accommodative acts.

Professor Weale has now demonstrated that an optical method, based on the study of birefringence and twice as sensitive as the mechanical method, can be used to measure mechanical stress in the lens. He finds a significant difference between the stress pattern in young and old lenses, the old lenses being much more sensitive to mechanical trauma than the young ones.

He now plans to use this method to investigate the effect of repeated small stresses to the young and old lens. He hopes to establish a relation between critical stress amplitude and number of stresses as a function of age. To carry out this important project he requires a special compressor, which would stress the lens by very small amounts once every two seconds or so for up to about 100,000 times. In 1978 the RNIB granted £4,144 for the purchase of the necessary apparatus.

Some of the equipment has already been used in a study of lenses which cover an age spectrum of almost 90 years. An incidental observation was that the biophysical properties of the lenses of the two sexes differ on a statistically significant basis. The study has led to two predictions:

- a) that there may be a correlation between senile cataract and ametropia, and also
- b) that there might be a higher incidence of cataract amongst women than amongst men.

Case studies have lent support to both predictions.

MOORFIELDS EYE HOSPITAL

In 1976-8 the RNIB granted Dr. Eva Kohner about £5,300 to assist her in her project, the quantitative evaluation of retinal capillary leakage in diabetes.

The aims of the study which was started in 1977 are three-fold:

1. To establish a quantitative method of measuring fluorescein leakage from retinal blood vessels by measurement of vitreous fluorescence.
2. To study the evolution of diabetic retinopathy by measurement of vitreous fluorescence.
3. To study the effect of 'excellent' diabetic control on vitreous fluorescence.

There were considerable difficulties with setting up the method:

- (a) the equipment as described by Cunha-Vaz (1975) was not sufficiently sensitive and required considerable improvements;
- (b) partly because of the unstable pound and partly because of extra equipment requested extra funds had to be found;
- (c) poor delivery dates (8/12 for 1 piece) and modifications which had to be introduced, delayed effective work.

However the modifications are now completed and a critical appraisal of the method as used by Dr. Kohner and Cunha-Vaz (1975, 1978) is in preparation; this almost invalidates the results of the originators of the technique.

Dr. Kohner and her collaborators have done repeatability studies on normals and diabetics with and without retinopathy. These, together with the methodology, will be submitted to the British Diabetic Association Meeting.

They have also undertaken a study of hydroxy rutoside in early maculopathy. This drug which on previous qualitative studies was said to reduce fluorescein leakage was used in 12 patients in a double blind crossover study. In summary: though somewhat slow in starting, the studies are now running smoothly and rewarding results are expected in the near future.

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- Cunha-Vaz J. Faria de Abreu J. R., Campas, A. J., and Figo G. M.
Early breakdown of the blood-retinal barrier in diabetes.
Brit J. Ophthal, 1975, 59, 649-656.
- Cunha-Vaz J. Fonseca J. R., Abreu, F. F., Ruas, N. A.
Early retinal involvement in diabetes.
Amer J. Ophthal, 1978, 467-474

POCKLINGTON EYE TRANSPLANTATION RESEARCH UNIT

Staff List

Co-ordinator: Professor Barrie R. Jones, BSc, MB, ChB,
FRCS, FRCP, FRACS

Clinical Director: Noel S. C. Rice, MD, FRCS

Senior Lecturer: Emil S. Sherrard, BSc, PhD

Visiting Fellows & Research Assistants:

D. O'Day	(Australia)	1971-72
D. J. Perriam	(Australia)	1972-73
W. J. Reinhart	(U.S.A.)	1972-73
J. McKinnon	(New Zealand)	1973-74
C. Breslin	(Canada)	1974-75
P. Cherry	(Canada)	1974-75
D. Coster	(Australia)	1974-75
L. Olson	(U.S.A.)	1975-76
G. Sturrock	(U.K.)	1976-77
I. Shepherd	(Ireland)	1978-79
T. Chin Fook	(Canada)	1978-79
A. Tokarowitz	(Canada)	1978-79

Technicians:

Grace Daniels	1971-74
G. Walters	1973-74
L. Ng	1974-

The back surface of the cornea is lined by a sheet of tissue which is composed of about $\frac{1}{2}$ million cells. These are arranged as a single layer and so the sheet has a thickness of only 0.005 mm. This endothelium is exceedingly delicate and responds unfavourably to the slightest changes in its environment. In Man, damaged endothelial cells are not replaced, and yet the integrity of this fragile tissue is essential to the transparency of the cornea and hence to vision. This is because each of its cells is an active (metabolic) fluid-pump which continuously removes fluid from the other corneal tissues against their tremendous inhibition potential. The passive inflow and active removal of corneal fluid must be exactly balanced because the minute arrangement of the solid components of the bulk of the cornea is dependent upon complex pressures so created and light transmittability is, in turn, dependent upon this arrangement. The corneal endothelium may be damaged due to disease or therapy - surgical and chemical. Clearly it is placed at great risk during corneal transplantation when it must withstand the effects of death of the donor, removal of the eye, transportation and banking and finally removal of the corneal disc and placement onto the host eye. Because of the singular importance of the endothelium in corneal transplantation, the work of the Pocklington Eye Transplantation Research Unit has focused upon this vital structure.

Some of the projects have been short-term and undertaken by Visiting Fellows from abroad, while others have progressed over the years. One such project has been the development of the specular microscope by Dr. Sherrard for both laboratory and clinical use. With this apparatus the endothelium can be seen at relatively high magnifications through the overlying corneal tissues and can thus be examined in its living state with no alteration in its environment to render it visible. The microscope is therefore invaluable in the evaluation of the condition of the endothelium of experimental and clinical corneae. By 1972, an admirable bench specular microscope had been developed for use in the laboratory and it is now used routinely in most of the research projects, while a clinical specular microscope, to be known as "The Pocklington" is to be marketed later this year by Konan Cameras Inc. of Japan in association with Keeler Instruments in London. Meanwhile, a prototype of this apparatus is routinely used at Moorfields Eye Hospital at City Road for the examination of the corneal endothelium of patients. To date, Dr. Sherrard has published two papers, contributed to two books and given several talks in the UK and USA on the development and techniques of specular microscopy.

The search for better methods to store donor corneae is another long term project. Various methods have been evaluated by experimental corneal grafting and specular microscopy, but so far no great advances have been made, although McKinnon published results showing that corneae submerged in horse serum containing antibiotics occasionally survived a day or two longer than when kept as whole eyes. Currently a re-evaluation of deep freezing corneae for prolonged storage is underway in association with the Cryobiology Unit, Douglas House, Trumpington Road, Cambridge. Since the method was last seriously investigated many advances have been made in cryobiological techniques and the Pocklington Unit is indebted to Drs. Pegg and Taylor of Cambridge for their expertise in this collaborative project. A reliable method of prolonged storage of donor corneae is essential if matching of histocompatibility antigens between donor and host is to become a practicable clinical possibility.

In 1973 a new method of short-term storage of corneae was developed in the USA and became known as the M-K method. Isolated corneae were stored in a specially formulated medium at 4 deg C. A similar method had also been actively studied in the Pocklington Unit for several years, but had failed to pass the rigorous testing needed to introduce it into clinical practice. Dr. Breslin subjected the M-K method to rigorous testing, but his results were disappointing as no real advantage over the orthodox banking of whole eyes was apparent. The criticisms supported by evaluation of the M-K stored corneae by specular microscopy, electron microscopy and experimental corneal grafting formed the basis of four publications jointly with Drs. Sherrard and Rice.

At the Ciba Foundation symposium in London in 1973 on "Corneal Graft Failure", Sherrard re-emphasised the possibility of employing specular microscopy as a means to evaluate the endothelia of all donor corneae immediately prior to their transplantation. Previously published animal experimental work had proved successful, and the aim was to eliminate the "rogue" cornea which may pass as suitable for grafting on other criteria. However, pursuit of the idea revealed that the formation of wrinkles in the deep layers of human corneae preclude this as a method. Nevertheless, the wrinkles and the cause of their formation are currently under investigation.

Specular microscopy and scanning electron microscopy were used by Dr. Olson to determine the effect of a relatively new technique of cataract extraction upon the corneal endothelium. The method - phacoemulsification - uses ultrasonic vibrations to disrupt the lens, and it seemed that owing to its closeness to the cornea some endothelial damage might result. In collaboration with Dr. Marshall of the Department of Visual Science at the Institute of Ophthalmology and Dr. Andrews at Charing Cross Hospital, Dr. Olson showed that ultrasound alone produced discrete lesions in the endothelium, and that these were recoverable by the spread and enlargement of the adjacent cells. This finding and related observations appeared in two publications in 1978. Recent modifications of the technique of phacoemulsification appear to have overcome the endothelial damage and Dr. Sherrard is currently engaged in the specular microscopical evaluation of experimental corneae.

All investigations employing animal eyes as models depend upon an awareness of any species specific variations in endothelial morphology and factors like ability and mode of repair. Hence Dr. O'Day studied the normal and traumatised corneal endothelia of laboratory animals and demonstrated that the endothelial cells of animals like the commonly used rabbit are capable of extensive and rapid division so that damaged cells are quickly replaced. He devised and published a useful method with which to evaluate the degree of cell division using radioactive isotopes. Specular microscopy has since confirmed Dr. O'Day's findings.

The clinical specular microscope permits the examination of the corneal endothelium in living subjects, animal or human, and may thus be used as a research tool to observe the response of the tissue to experimental changes, or for diagnosis and the determination of pathological changes. Dr. Sherrard has observed endothelial changes in vivo as a result of the use of clinically used agents and reported some of the findings at the III World Congress on the Cornea in Washington DC in 1976. Additionally, he has published studies which reveal flaws in previous investigations which employed methods of evaluation of the endothelium other than specular microscopy. The ability to observe the endothelium of living subjects allows each experiment to be conducted on the same endothelium, without the need to interrupt it in order to prepare the specium for histological or electron microscopical examination with attendant artefacts. Hence the effects of each experimental procedure can be followed in toto and repeats of the same procedure may be arrested and studied by alternative methods at visually determined, rather than arbitrarily selected, stages. In vivo specular microscopy has therefore revealed misinterpretations due to artefact of preparation. Observations showing the effects on the endothelium of cooling, fixation, and irrigation of the anterior chamber have been published. Moreover experimental corneal grafting in rabbits as a means to demonstrate the survival or otherwise of an experimentally stored cornea has been shown to be unreliable. This casts doubt on some older reported results.

More recently the finding of a specular microscopical study of the corneal endothelium of normal human eyes in vivo has been published by Sturrock, Sherrard and Rice. The purpose of the study was to determine "what is a normal human endothelium?". The factors investigated were: the average number of cells per endothelium; natural changes associated with ageing; comparisons between the endothelium in the central and peripheral areas of the same cornea, between the two eyes of the same subject, and over a period of time. In general it was found that the endothelium is similar in all areas of a cornea and in the eyes of a pair, but there is much variation in cell number, size and shape between individuals with a tendency to a reduction in number with

increasing age. With this information, Buckley and Sherrard are studying the endothelial changes associated with disease in human patients with a view to earlier diagnosis once experience has been acquired and the various endothelial changes have been photographically recorded "translated". In addition, the adverse effects, if any, of various ocular surgical procedures upon the endothelium are being studied by "before and after" photomicrographs.

Drs. Perriam and Reinhart developed a model of graft rejection in the rabbit cornea and showed in a very extensive set of experiments that the drug promethazine delayed the onset of graft rejection in high risk corneal transplants and that in some cases, where vascularisation of the host cornea was not excessive, rejection was prevented altogether. This work was performed jointly with the Pocklington Eye Transplantation Research Unit and May and Baker Limited in 1972-73.

A similar, though independent, series of experiments has just begun in the Unit by Drs. Shepherd and Chin Fook to determine the immunosuppressive effect of a new drug - Cyclosporin A.

Other current projects concern the basic physiology of the cornea. Dr. Tokarowitz is investigating a claim from the Welsh National School of Medicine that corneal endothelium actively moves bicarbonate ions from the cornea and that this is the basis of the endothelial 'pump'. Starvation of bicarbonate "switches off" this 'pump', and this may be of importance in the storage of donor corneae which may then be banked in an almost quiescent state.

Dr. Cherry, in association with Dr. Garner of the Department of Pathology at the Institute of Ophthalmology investigated the use of the argon laser to occlude corneal blood vessels. The normal cornea is avascular but in many pathological conditions blood vessels grow into the stroma. Their presence disrupts corneal transparency and complicates corneal grafting by raising considerably the risk of rejection of the graft. It was found that the argon laser treatment effectively 'stopped' these vessels, but that both arteries and veins had to be treated and that usually some damage to the iris was unavoidable. The Hammersmith Hospital allowed us use of the laser which was donated by the Medical Research Council.

In certain pathological conditions deep scarring of the cornea results but the endothelium and a very thin supporting (Descemet's) membrane remain unaffected. It was felt desirable, therefore, to develop a method of stromal replacement leaving the host endothelial and Descemet's membranes intact. Sherrard developed such a method, and it is now used world wide in laboratory investigations since it provides 'clean' specimens of almost naked corneal endothelium for study.

Although specular microscopy has now become a routine procedure in both laboratory and clinic, the interpretation of what is seen remains. Certain endothelial changes can be produced experimentally and many of these affect scattered cells only. Thus a technique has been developed by Sherrard which allows the relocation of just one of the damaged cells among the $\frac{1}{2}$ million or so to be relocated in stained, histological preparations taken from the same cornea.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

D. W. Hill, FRCS Research Professor, Department of Ophthalmology,
 Royal College of Surgeons
 S. Young, AIMBI, FIIP, Senior Technician, Photographic

Associated Research Workers:

Dr. L. T. Laatikainen	1975-76
Dr. H. A. Atherton, PhD	1977 onwards

Visiting Research Worker:

Dr. E. F. Cherney, MD	1978
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Collaborators:

Dr. A. J. Barnes, MRCP Royal Postgraduate Medical School
 Professor H. Keen, FRCP Guy's Hospital Medical School
 Dr. E. M. Kohner, MD, MRCP Royal Postgraduate Medical School

Studies of the Retinal Circulation

Diseases of the retinal blood vessels which impair the circulation and consequently the nutrition of the retina form an important category in the list of causes of blindness; perhaps the most important cause of blindness in this group being diabetic retinopathy. In recent years a significant advance has been made in clinical practice by the use of two techniques, fluorescein angiography, for diagnosis, and photocoagulation, for treatment. There remains, however, a serious lack of knowledge about the normal physiology of the retinal circulation and its reaction to disease and therapeutic interference. During the period under review Professor Hill and his colleagues have been working in the laboratory to elucidate some of the aspects of the physiology of retinal circulation, with the aid of grants received from the RNIB and other sources.

By using the technique of high speed cine angiography it has been possible to investigate the rate of blood inflow into the retina and to measure the decline of linear flow rate as blood passes centrifugally into an expanding vascular bed. The rate of blood flow per unit area of retinal tissue has also been found to decline on passing centrifugally; and calculations show a slower rate of blood flow in the peripheral retinal capillaries.

The effects of photocoagulation on the distribution of retinal blood flow have been and continue to be studied, an investigation of great importance to the understanding of this method of treatment. Collaborative work has been carried out with other investigators on the effects of altered blood viscosity in the retinal circulation, also of importance in relation to clinical disease. In a joint project the effects of altered blood glucose levels (as experienced in diabetes) and other metabolites are being studied.

ROYAL EYE HOSPITAL, LONDON

A. I. Friedmann, FRCS Consultant Ophthalmologist
 Mrs Claringbold, Ophthalmic Technician
 Miss F. Graham, Secretary

Mr. Friedmann has received financial support over the past years from the RNIB to enable him to pursue four research projects:

1. Blind Schools and Institutions

Two papers have been read related to the "Blind School" material investigated over the past 10 years or so. The first dealt with the genetic causes of severe visual handicap and in the second a more extensive analysis of all causes of severe visual handicap was made. This analysis revealed that in a large number of cases the visual defect was associated with perinatal morbidity.

A computer analysis of human polymorphosis investigations on families with clear cut dominant and linked inherited eye disease was made. No linkages or associations with normally occurring blood constituents, including many blood groups and haemoglobins could be shown.

Mrs. Claringbold is involved in an investigation of some aspects of the biochemistry of retinitis pigmentosa, at the Department of Biochemistry at the Institute of Ophthalmology, London.

2. Development of Ophthalmic Instrumentation

One of the most important examinations done by Ophthalmologists, Opticians and Neurologists is the visual field examination. The Visual Field Analyser, devised and developed by Mr. Friedmann, has become one of the more important instruments used all over the world. Perhaps its most important applications are in Glaucoma and Neuro-Ophthalmology. But there are many others including the ocular drug toxicities.

Over the last three years intensive research work and collaboration with the manufacturers of the analyser have led to the development of a second generation analyser, Mark 2.

A production prototype of the Mark 2 Analyser was taken by Mr. Friedmann to the Bascom Palmer Eye Institute in Miami, Florida. Here a preliminary research project was undertaken by Dr. Anderson and staff of the Institute Glaucoma Clinic and Mr. Friedmann to compare the effectivity of the visual field techniques employed there and the Mark 2 Analyser in cases of early glaucoma.

Further work needs to be done before final conclusions can be made and published. The results will have important implications for the clinician.

3. Glaucoma

This is a continuing topic of research, not least the visual field aspects, because this examination is essential in both the diagnosis and management of the disease. A number of papers have been read by Mr. Friedmann on the analyser and its use in a variety of conditions including glaucoma. It is gratifying that some of the leading Authorities now believe that the basic techniques of the analyser are the best in the early diagnosis of this disease.

A project has been completed with the Department of Pharmacology of St. Thomas' Hospital to evaluate the advantages of Ocuser pilocarpine (a slow drug release system) compared to pilocarpine drops in cases of glaucoma. This paper has been completed and is being submitted for publication.

4. Tuberculosis and Ethambutal

Mention has previously been made of the British Medical Research Council Tuberculosis and Chest Units Study of Spinal tuberculosis in South Korea, using among others, the anti-tuberculous drug, Ethambutal.

Because the safe, effective dose of drugs in children is not yet known (it may damage the optic nerve), this study will probably become the international "blue-print" for the use of Ethambutal in children.

The MRC asked Mr. Friedmann to go to Korea about 3½ years ago to set up a system that would detect optic nerve damage early enough to stop permanent damage to vision. Unless this was done the Study could not be set up. The monitoring system was set up in Korea and since then Mr. Friedmann has been back twice to examine patients and check the monitoring system. The project has another 18 months to run. Future studies are being discussed with the Department of Pharmacology at St. Thomas' Hospital, where there is a very sophisticated pupillometer. This is particularly useful where pupil size measurements are important, as in both chronic open angle and closed angle glaucoma.

ROYAL SALOP INFIRMARY, SHREWSBURY

Dr. P. R. Hunter, MA, MB, MRCP, Consultant physician

Dr. S. Al Windawi, MRCP

RNIB Full Time Research Registrar in Diabetic Retinopathy (for a period of one year)

Dr. Alex Wright, FRCP (C)

Senior Lecturer in Medicine and Consultant Physician, Birmingham General Hospital

During the years 1974-1976 the RNIB supported the research of Dr. Hunter and his colleagues, into various aspects of diabetic retinopathy. Five projects were undertaken.

Project 1

They aimed to develop a standardised and reproducible method of measuring cutaneous capillary resistance (CCR) in order to test the capacity of drugs to raise CCR in diabetics. Capillary resistance is known to be low in diabetics with severe retinopathy, their capillaries being abnormally fragile.

The investigation established that in only three out of fifteen diabetics with severe retinopathy were serial CCR readings sufficiently reproducible to permit reliable detection of the effect of a drug on CCR. This methodological problem has not been taken into account in any previous publication on the effect of drugs on CCR in diabetics.

Project 2

Development of a standardised procedure to test drugs for their capacity to reduce exercise induced growth hormone output in diabetics.

This procedure was developed together with Dr. Alex Wright at the Birmingham General Hospital. The drug Pimozide was tested out in diabetics with and without retinopathy and in normals. It was found that Pimozide did not reduce exercise induced growth hormone output in diabetics.

Project 3

A review of the world literature on CCR relating to suction and diabetic tissue damage, including a review of endocrine aspects of this subject was prepared. This is the most extensive review on the subject that has been written. (Potentially important inference about drugs that could benefit diabetic retinopathy but which have not been the subjects of clinical trials are derived from this review). Copies are available from Dr. P. R. Hunter, Royal Shrewsbury Hospital North, Mytton Oak Road, Shrewsbury. It is hoped that part of this review will be published in Diabetologia.

Project 4

They attempted to develop a photographic method to increase sensitivity of CCR measurements, in order to assist in the clinical testing of drugs that might raise CCR in diabetics. The main conclusion of this study was that it was probably feasible but only with the extensive collaboration of a professional photographer.

Project 5

A study of the effect of duration of diabetes on capillary resistance was pushed forward but has not yet been completed.

THE QUEEN'S UNIVERSITY, BELFAST
ROYAL VICTORIA HOSPITAL, BELFAST

Department of Ophthalmology

Desmond B. Archer, Professor of Ophthalmology
Hugh McGalliard, DSc
Thomas Gardiner, AIMLS

In 1977 the RNIB gave £3000 to the Department of Ophthalmology to assist with the purchase of its own ultramicrotome. This equipment has already been profitably used on three projects concerning the ultra-structure of certain parts of the eye. The development of retinal vein collaterals in the Rhesus Monkey has been studied, after occlusion of tributary veins. An animal model (Rhesus Monkey) of new retinal and choroidal blood vessels has been developed over the past three years and recent work has revealed a number of unusual intracytoplasmic membranes organelles in the endothelial cells of the new choroidal vessels and these are currently being examined and documented. Thirdly, an ultrastructural study of the endothelial cells of human umbilical veins at various stages of maturation has been initiated. The intracellular organelles of these cells are being compared with those of new vessels provoked by retinal ischaemia.

ST. BARTHOLOMEW'S HOSPITAL

J. H. Dobree, MS, FRCS, Consultant Ophthalmic Surgeon

In 1974 the RNIB purchased a vitrectomy Instrument for Mr. Dobree, and his collaborators.

To start off with there was considerable difficulty in getting the instrument to work properly as the American manufacturers failed to supply instructions for assembly. However, they finally got it working but this time the original research which had been planned was no longer appropriate. They had originally hoped to research into the problem as to whether vitreous haemorrhages were best treated,

- (1) by removing the vitreous with a clot in situ,
- (2) by attempting to dissolve the clot using Urokiase, or
- (3) by simply waiting to see if the haemorrhage cleared spontaneously.

By the time the Vitrectomy instrument was functional, they had already produced evidence based on some two years' observation of fifty patients that conservative measures appeared to be at least as effective as reported cases of removal of the vitreous. They were, therefore, limited in the use of the apparatus and confined it to a few cases only. These were all cases in which the prognosis was poor and, in fact, did badly surgically.

On the credit side, however, they have found the instrument of considerable use in surgery of the anterior segments of the eye, particularly cases involving trauma to the iris and lens. The use of the instrument has developed more into a service apparatus rather than a research tool. In the past two years or so, there have been many reports of the use of what were originally intended to be vitrectomy instruments proving to be of great value in operations on the iris and crystalline lens.

ST. THOMAS' HOSPITAL MEDICAL SCHOOL, LONDON
UNIVERSITY OF LONDON

A. H. Chignell, FRCS, Consultant Ophthalmologist
T. J. Ffytche, FRCS, Consultant Ophthalmologist
John Shilling, FRCS

Department of Pharmacology:

Dr. S. E. Smith, Reader in Applied Pharmacology
Dr. Shirley A. Smith, MRC Research Fellow
Dr. C. J. K. Ellis, Research Registrar
Dr. R. Ponsford, Registrar in Neurology,
St. Mary's Hospital, Paddington, London, W.2.

In association with medical colleagues at St. Thomas' Hospital and elsewhere.

Vision Research Unit:

Hisako Ikeda, Head of Unit

Other people who were associated in the research are:

Dr. M. J. Wright	1972-1975
Dr. G. Einon	1977
Dr. K. E. Tremain	1976-1978
Dr. G. Plant	1975-1977
Mrs Janet Turner	1972-1978
Mr. John Dench	1972-1976
Mr. Brenton Hodelin	1976-1978
Mr. John Muckelroy	1978
Mr. Gary Davis	1978
Mr. H. Reyford	1977-1978
Mrs. J. Wilkes	1978

Mr. Chignell and his collaborators have investigated the treatment of diabetic retinopathy, especially using Argon laser photocoagulation, and several independent trials have been set up to test the efficacy of this method of treatment. They have been particularly interested in assessing the complications of Laser photocoagulation as opposed to Xenon photocoagulation, and they are also attempting to decide how much treatment is necessary to induce regression of new vessel formation. In addition to these purely ophthalmological aspects of the treatment of diabetic retinopathy, they have also worked closely with the physicians at St. Thomas' Hospital in their active programme of diabetic research. They are attempting by various haematological investigations to identify the role of control of diabetes, and to see what influence this has on retinopathy in some of the most difficult cases.

Research has been conducted along three main lines:

(1) Glaucoma

Work done has involved exploring the action of two novel delivery systems for pilocarpine application to the eye, whereby control of intraocular pressure is made more continuous than with conventional eye-drop therapy and more convenient and easier for the patient. The rationale for this is to improve the patient's compliance with his medication and thereby in the long term to help save his sight. Subsidiary investigations have been done to find out more about drug penetration into the eye and about long-term effects of pilocarpine and other similar drugs. A new line of research has been started in the control of glaucoma with adrenoreceptor blocking drugs (β -blockers) such as pindolol. These drugs appear to lower intraocular pressure effectively without impairment of vision through drug effect on the pupil or the ciliary muscle. This is a promising field and further work on long-term drug influence is planned.

(2) Diabetes

A major project in co-operation with diabetologists has been completed. It shows that in diabetes the pupil is reduced in size and reactivity and that there is a strong association with neuropathy affecting other parts of the body. Whether the pupillary abnormality is due to neuropathy is not yet known, but some drug tests are planned which aim to elucidate this matter. It is also planned to investigate the influence of intensive diabetic control on pupillary signs and on neuropathy to see if these abnormalities are potentially reversible.

These studies are not primarily related to the blindness caused by this disease but to the fundamental changes produced in nerve function which are so often associated with it.

(3) Physiology and Pharmacology

This area is concerned with fundamental aspects of pupillary function and mechanisms underlying the light reflex response. Because of the novelty of the techniques involved, much of the work done so far has been directed at defining the characteristics and the limits of normal function. It is anticipated that investigations of more immediate practical relevance to the treatment of disease will take the place of these basic studies within the next 12 months or so.

Vision Research Unit

This Unit was founded in 1969 and moved to the Rayne Institute of St. Thomas' Hospital in 1976. The RNIB has given financial support from 1973 to 1978, for successive electronic technicians, John Dench and Brenton Hodelin.

Studies on the neurological basis of visual acuity and strabismic amblyopia have shown:

- (1) A special class of retinal cells packed at the fovea and the cells in the brain which receive the inputs from these foveal cells have the property of high spatial resolving power, whereas the cells in the peripheral retina are poor in spatial discrimination, but excellent in movement detection.

- (2) The visual acuity of the fovea is poor at birth, but rapidly develops to the adult level during early life and stimulation of the fovea by sharply focused images is essential to accomplish this development.
- (3) If the fovea receives poorly focused images of the outside world due to squint, high refractive error, cataract, or lack of ability to fixate (abnormal foveation) during this crucial period of development, the visual acuity will never become high enough to resolve small objects in detail (arrest of development), and the eye will become amblyopic.
- (4) The lack of binocular vision and the loss of visual acuity have different causes in strabismic cases. The loss of visual acuity in the squinting eye is due to arrest of functional development of the foveal retinal ganglion cells, whereas the loss of binocular vision is due to the difference in the activities arising from the two eyes and its lesion is in the brain.
- (5) These findings suggest that refractive errors or squint must be corrected as early as possible in childhood, in order to prevent amblyopia (poor visual acuity) in later life.

An investigation was made of many patients who have been diagnosed as having optic nerve disease by using retinal and visual cortical electrophysiological techniques. It was shown that differential diagnosis could be made for:

- (a) Patients with demyelinating disease such as multiple sclerosis or inflammation of optic nerve (optic neuritis).
- (b) Patients with optic nerve compressed by pituitary tumour.
- (c) Patients with toxic amblyopia caused by excessive drinking or smoking, and
- (d) Patients who show atrophy of the optic nerve for unknown reasons.

An important discovery is that many of the patients who showed the optic nerve disease also showed reduced retinal function at later stage.

SHEFFIELD CITY POLYTECHNIC

I. L. Freeman, BSc, ARIC, MI Biol
D. A. Leathard, MA, PhD, ARIC

Financial help was given by the RNIB to support a Research Assistant. The research project concerned the protein-bound carbohydrates of the lens. There is evidence that glycoproteins are involved in the aggregation of collagen fibres, and that this could also be the case for the proteins of the lens fibres. The aim was to isolate, identify and quantify the carbohydrate moiety of the lens glycoproteins, to aid the interpretation of the role of these macromolecules in ageing and disease.

Lens tissue glycoprotein contains not one but many different types of carbohydrate, such as glucose, galactose and sialic acid. In this work, therefore, sensitive methods of separation and detection were developed, allowing the various types of carbohydrate molecule to be stripped from the protein and individually identified and measured. The individual carbohydrate profiles obtained in this way provided more information than could be obtained by simply measuring total carbohydrate content. Thus small differences between glycoprotein samples could be detected.

This work was unfortunately not completed because Dr. Freeman left Sheffield for the USA.

UNIVERSITY OF ASTON IN BIRMINGHAM

Department of Ophthalmic Optics

N. Drasdo, BSc, FBOA, Senior Lecturer

I. J. Murray, BSc, MSc, FBOA, Visiting Lecturer

Department of Ophthalmic Optics, University of Aston

Field Expanders for Patients with Tunnel Vision

The normal visual field extends over approximately one third of the total surrounding environment. In some conditions, notably in retinitis pigmentosa, the size of the visual field may be contracted so that vision only occurs over a narrow angle of perhaps 5-20 deg. around the point at which the subject is looking. This is described as tunnel vision, and is found to have a very disabling effect. Studies have been conducted on the nature of the difficulties experienced by patients with tunnel vision and on the theory and development of optical systems, known as visual field expanders, which are designed to counteract the disability.

The loss of mobility, the difficulties of orientation and visual search for small misplaced objects such as keys or coins, the hazards and other difficulties of patients suffering from tunnel vision have been investigated by questionnaires and interviews. Data on the visual search capabilities of such patients were further investigated with the aid of a visual performance task.

Some new optical designs have been produced with the aim of rendering the field expander so minute as to be inconspicuous, without sacrificing the sharpness of linearity of the image. Some success has been achieved and the device is sufficiently small to allow the possibility of continuous wear since the patient can look through the system or past it in order to obtain normal sized image. It has been shown that there is some theoretical basis for supposing that extreme cases of tunnel vision can roughly simulate the effect of the normal visual field by rapid alternative fixations through the field expander and its surround with such miniaturised designs, providing that the visual acuity of the patient is good centrally. Such fixations can occur at the rate of more than two per second.

It has been concluded that the continuous wear field expander must still be regarded as an experimental device but subject to certain development and some more evidence of clinical value this could become a routinely dispensable item. On the other hand a hand-held pocketable system may be worthwhile for occasional use. In this instance specially constructed systems are unnecessary since a reversed-Galilean telescope or door-spy system is small enough and cheaply available.

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UNIVERSITY OF BRISTOL
BRISTOL EYE HOSPITAL

Department of Surgery, Bristol Royal Infirmary
David L. Easty, MD, FRCS, Consultant Ophthalmic Surgeon
Clare Carter, BSc

In 1976 the RNIB made a grant to Mr. Easty to pay the salary of Miss Carter, a PhD student, for 3 years. Their research project was to assess whether immunological factors have therapeutic efficacy when applied topically to the eye infected with herpes simplex virus.

Herpes simplex keratitis is one of the most common infectious diseases of the cornea in Britain. It is a recurrent infection, as is the case with the cold sores caused by the same virus (HSV). In the cornea, the infection is not only disabling for the duration of the recurrences (which can be very frequent), but it can also lead to loss of vision due to permanent scarring, which may need to be treated by a corneal graft.

Professor Easty and Miss Carter have concentrated on ways of inhibiting the virus infection, as decreasing the severity of frequency of recurrences would reduce the risk of these complications occurring.

Although the cornea is often considered largely isolated from the immune system, it has been found that systemic immunity has a great influence in protecting the cornea from HSV infection. Since most patients are already immune to HSV, this may mask the effect of the standard antiviral preparations. Eyedrops containing high concentrations of antibody to the virus have been found to be very effective when commenced at the beginning of infection. The possible value of these preparations lies in their probable lack of toxicity to the cornea, so that they might be used over long periods to prevent recurrences. These studies are continuing.

The enhancing effect on corneal HSV infection of corticosteroid drugs has also been studied, as this is a serious complication in the treatment of herpetic keratitis. The lowest "steroid" concentration of the clinically used range has been found not to cause any apparent enhancement, in comparison with higher dosages where the degree of enhancement increased in proportion to the drug concentration.

UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, LONDON

H. Heath, Dsc Phd BSc FRIC
 R. P. Boot-Handford BSc
 Y. C. Hamlett PhD BSc
 S. S. Kang PhD BSc
 D. Papachristodoulou PhD MSc BSc
 R. A. Paterson PhD BSc
 J. Pollock PhD MSc BSc
 R. Poulson BSc
 J. Stewart PhD MSc BSc
 R. M. Totterdell BSc

Irving K. Luke FRCS DCH DO

Department of Biochemical Pathology

In 1976 research was started in this laboratory to investigate the role that blood platelets might play in the aetiology of diabetic retinopathy. It was shown that the platelets were abnormal in patients with advanced retinopathy and since then much research has been carried out in other centres, but it has not yet been possible to prove whether these observed changes are causal or secondary to the pathological state of the vascular wall in the human diabetic. Studies have, therefore, been carried out by Dr. Paterson on the intermediate metabolism of platelets obtained from normal and diabetic rats and by Dr. Pollock on the ability of certain flavonoids to modify the activity of rat platelets in vivo with a view to finding a drug for the prophylaxis of diabetic retinopathy.

In 1973 the British Foundation for Research into the Prevention of Blindness awarded Dr. Heath a grant of £15,000 (generously donated by the Clothworkers' Company, the RNIB and the Trustees of the Will of Lord Austin Deceased) over three years to study the effects of a high dietary intake of sucrose on the development of retinopathy in experimental animals. Normal and streptozotocin-diabetic rats have been maintained for up to 11 months on synthetic diets in which the carbohydrate source was either 68 per cent cornstarch or 68 per cent sucrose. The retinal vascular system was isolated by trypsin digestion and examined histologically for the presence of tortuosity and irregularity of capillary diameter, increased PAS-positive deposits, microaneurysms, loss of pericytes, endothelial proliferation, acellularity and strand formation.

The retinal vascular systems from the non-diabetic rats fed on a starch-rich diet were found to be completely normal, whereas the above pathological changes developed to a similar extent in the sucrose-fed non-diabetic rats as well as in the starch-fed diabetic animals. The changes were more severe in sucrose-fed diabetic rats after six months and in both groups the retinopathy progressed with time. Since, histologically, the retinopathy observed was identical both with respect to severity and rate of development in normoglycaemic, sucrose-fed and hyperglycaemic starch-fed diabetic rats, the possibility exists that there is a factor common to both the ingestion of a sucrose-rich diet and streptozotocin-diabetes.

Biochemical studies have also been carried out on similar groups of animals and it was found that there was a significant increase in the lactic acid content and the lactate-pyruvate ratio in the retinæ of diabetic rats and in those from the sucrose-fed animals. Sucrose is a disaccharide of glucose and fructose and it was thought that the observed increased production of lactic acid might be derived from the fructose moiety. If so, this would provide a possible link between sucrose-induced and diabetic retinopathy, since during periods of hyperglycaemia in the diabetic, glucose is metabolised by way of the sorbitol pathway. The presence of this pathway in the retina has been established by Dr. Hamlett who showed that the sorbitol and fructose content of the retina was increased in the diabetic state, and in further histochemical studies established the presence of sorbitol dehydrogenase in the rat retina. Weight was also added to the hypothesis by the demonstration that fructokinase, a specific enzyme involved in this process, is present in the rat retina and that increased concentrations of fructose-1-phosphate occur.

There has been much controversy as to whether basement membrane thickening precedes the occurrence of overt diabetic microangiopathy and electron microscopic examination of the retinas from these animals has, therefore, been carried out by Dr. Papachristodoulou. Perpendicular cross-sections of 15 capillaries from the retinal outer plexiform layer from each animal were examined qualitatively and quantitatively. Ramifications of the basement membrane nodules and deposition of collagen-like material within the basement membrane from the sucrose-fed normal animals were observed, but no uniform thickening took place. Similar pathological changes were present in the diabetic capillaries except that a significant increase in the thickness of the basement membrane occurred. This thickening was not related to either blood glucose levels or the severity of the retinopathy, indicating that the development of retinopathy, at least in the sucrose-fed animals, is not related to basement membrane thickening, but rather to the deposition of material within the membrane.

In 1976 a further grant of £18,000 (generously donated by the British Diabetic Association, the Clothworkers' Company, the RNIB and the Trustees of the Will of Lord Austin Deceased) was made by the British Foundation for Research into the Prevention of Blindness to Dr. Heath to determine whether the fructose moiety of sucrose was, in fact, responsible for the development of retinopathy and whether diabetic retinopathy could be prevented by blocking the sorbitol pathway. Normal and diabetic rats have, therefore, been maintained on diets in which the carbohydrate source was either cornstarch, sucrose, glucose, fructose, whole cereal or an equal mixture of cereal and fructose. Retinopathy developed in all the non-diabetic animals fed on any of the diets containing fructose, but not in those fed glucose-containing diets; the diabetic rats, however, developed retinopathy when maintained on glucose-containing regimens. Microangiopathy was pronounced also in the kidneys of the fructose-fed rats. The first step in the sorbitol pathway is the reduction of glucose to sorbitol, catalysed by the enzyme aldose reductase. Diabetic rats are now being treated with an aldose reductase inhibitor to determine whether this will prevent the onset of retinopathy and nephropathy. These vascular complications only develop slowly, which necessitates the setting up of long-term experiments. Biochemical studies are also being carried out to determine whether sorbitol, fructose, fructose-1-phosphate and lactic acid formation is reduced not only in the retina and kidney, but in the lens and sciatic nerve.

In human diabetic retinopathy there is a loss of endothelial cells from the affected capillaries. It is thought that fructose is generated within these cells from glucose via the sorbitol pathway during periods of hyperglycaemia in the diabetic state. It has not been possible to isolate viable human retinal vascular endothelium, but cultures of human umbilical cord vein endothelial cells are being used to determine whether the sorbitol pathway is operative in these cells and whether this route for the metabolism of glucose can be blocked by the aldose reductase inhibitor.

If the above hypothesis is correct, it should be possible to prevent the development of many of the long-term complications of diabetes by the relevant chemotherapy.

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Mr. Irving Luke has continued to study the retinal vascular bed by fluorescein angiography in selected diabetic patients who, when first seen, had no clinical evidence of diabetic retinopathy. Some patients initially had angiograms performed at monthly intervals in the hope that it might be possible to recognise areas of transient capillary bed closure. In spite of the production of some high quality angiograms, no areas of transient closure could be identified.

All patients have had angiograms performed at intervals of approximately six months, some patients having had fifteen or more. Unfortunately, some patients who initially indicated a willingness to have photographs taken at regular intervals have ceased attending because they no longer visit the Diabetic Clinic at University College Hospital; one patient has died as a result of a cerebrovascular accident, but cumulative results are available on twenty-four patients.

The outstanding feature which the findings indicate is the very slow progression in clinical changes which have occurred since the onset of the study in 1970, for in only two patients have the angiographic features rapidly progressed. Significantly, both these patients became hypertensive after the study commenced.

In a further study, photographs have been taken of the conjunctival circulation of most of the patients and although it proved possible to recognise sludging of the circulation, it has not been possible to correlate conjunctival vessel appearances with severity of retinal change.

UNIVERSITY OF EAST ANGLIA
SCHOOL OF BIOLOGICAL SCIENCES

George Duncan, BSc, MSc, PhD
Andrew Bushell,
Leslie Patmore, BSc

The RNIB have provided financial assistance to Dr. Duncan over the years 1973-1978 in his research on Senile Cataract. He and his collaborators have studied the interactions of lens proteins with ions and made a number of important findings. It had been shown before that the level of sodium reaches very high values in mature cataract; Duncan confirmed and extended these observations and also found that the calcium concentration increased dramatically, sometimes to a hundred times its normal value, whereas that of magnesium (a similar divalent ion) remained unaltered. Further analysis of the distribution of calcium within the cataractous lens revealed that, unlike sodium, much of the calcium appeared to be bound to the lens matrix. In normal lenses the calcium was located primarily in the protein fraction soluble in water, whereas the large amounts of calcium that entered during the development of the cataract were bound mainly to the water-insoluble protein fraction; this fraction increases enormously in many cataracts. Duncan considers that calcium accumulation is primarily due to the breakdown of membrane permeability barriers. However, for accumulation to occur, binding sites with a very high affinity for calcium must be present. In fact he makes the intriguing suggestion that the water-insoluble proteins of the lens may bind as much calcium as muscle protein, which is believed to have evolved a special calcium binding capacity. These experiments are proceeding with the continued support of the RNIB.

UNIVERSITY OF OXFORD

Nuffield Laboratory of Ophthalmology

A. Pirie, MA, PhD
 R. van Heyningen, MA, DPhil, DSc
 J. J. Harding, BA, PhD
 J. M. Tiffany, MA PhD

L. R. Croft, BSc, PhD
 K. J. Dilley, BSc PhD
 J. C. Moore, BSc
 N. A. Panjwani, BSc, DPhil
 C. Slingsby, BSc, DPhil
 P. Trayhurn, BSc DPhil

During the period 1972-1978 the Nuffield Laboratory of Ophthalmology has received financial support for five separate projects. Two were new projects, a study of corneal collagen and studies of the precorneal tear film. The other three concerned the lens and senile cataract and were the last years of work started earlier and outlined in the previous booklet, 1967-72.

Studies on Corneal Collagen

Dr. Harding received a grant to support a DPhil student, Miss Panjwani, for three years to investigate the bound hexose of corneal collagen.

Collagen is the major protein of the cornea. Fibrils of corneal collagen are unusually fine and uniform and are arranged in an ordered array essential for transparency. The fibres of the opaque and tough sclera are thicker and less uniform. Fibrils of corneal scars are intermediate between these. Corneal scars and opacities occur frequently, are permanent, and entail gross visual disabilities. At present the only effective treatment is to remove the scar and to graft in its place part of the cornea of a donor. It is necessary to understand the nature of the unusually fine fibrils in the normal cornea, to be able to appreciate the changes that take place in scarring.

The molecular state of collagen varies according to its location. In general the collagen that consists of thick fibrils has a low glucoside content, whereas collagens consisting of fine fibrils and non-fibrillar collagens have high glycoside contents. The fine fibrils of corneal collagen contain a high proportion of hydroxylysine glycosides, and there is some evidence that the thicker fibrils of corneal scars have fewer glucosides than normal collagen. In rat skin the glycoside is located in the alpha 1 chain of the collagen molecule, about 10 per cent of its length from the amino-terminal end and is thought to fit into an axial hole present in that region. 'Extra' glycosides of the other collagens such as that of the cornea may not be in the 'hole' region and could therefore prevent close packing of large diameter fibrils. To understand the formation of the unusually fine fibrils of cornea, and to evaluate the role of hexose in corneal scar formation it is important to determine the location of hexose along the triple helices of collagen, especially in relation to the axial holes.

The problem was tackled by breaking down the collagen to peptides, using cyanogen bromide which cleaves at the methionine residues. The peptides made in this way were identified and examined using amino-acid analysis, gel electrophoresis and other techniques.

Miss (now Dr.) Panjwani was able to locate the position of nearly all the carbohydrate units of corneal collagen, firmly or tentatively, in this way. This work is part of an essential analysis of the structure of normal corneal collagen, paving the way to later studies of the scarred tissue.

Studies on components of the precorneal tear film

In December 1977 the RNIB gave Dr. John Tiffany £4,520 to purchase a gas-liquid chromatograph, for use by himself and his DPhil student, Mrs. Joan Moore, to study components of the precorneal tear film. The stability of this film is of the utmost importance in maintaining the health and transparency of the cornea, since gas exchange with the tears is a major metabolic route for the corneal epithelium. Apart from the aqueous secretion of the lacrimal glands, the tear film is known also to contain the oily secretion of the meibomian glands and mucins secreted by the conjunctiva. The stability of the tear film depends upon its composition; instability leads to more rapid drainage and formation of dry spots, and in extreme cases to conditions such as keratoconjunctivitis, and xerophthalmia, which may involve conjunctival adhesions, corneal opacity and eventual blindness.

Analysis of the meibomian lipid of the rabbit has shown it to be principally composed of a relatively small number of wax esters and sterol esters; these contain very long-chain saturated, branched fatty acids and alcohols, and some unusual sterols. Studies are in progress on the influence of these components on the melting and viscous properties of meibomian secretion, and their contribution to control of evaporation from the tear film. The composition of human and rabbit conjunctival mucus and tears has also been studied. In both cases the mucus contains disulphide-linked complexes of very high molecular weight formed from a mucous glycoprotein of about 200,000 MW containing 50-90 per cent carbohydrate in many oligosaccharide side chains 2-6 sugars long. A soluble mucous glycoprotein of similar size is produced by the lacrimal gland. Differences in sugar ratios and degree of sulphation have been detected between normal mucus and that secreted following irritation of the conjunctiva with ammonia vapour, and are being related to changes in the physical characteristics of mucus in dry-eye patients.

The human lens nucleus in Cataracta Brunescens

Dr. Dilley took over from Dr. Buckingham for the last year of a three-year research project, supported by a grant from the RNIB to Dr. A. Pirie. The subject of the research was the nature of the brown material in the human cataractous lens. By various chemical techniques they were able to separate a very dark brown amorphous substance that had an unusual fluorescence spectrum; it had a low nitrogen content inconsistent with its being entirely protein. They were not able to determine the nature of the brown material, but made an important advance in this difficult problem, that is now the subject of research all over the world and has still not been solved.

Protein breakdown in the lens

The RNIB gave a grant to Dr. van Heyningen to support a post-doctoral worker, Dr. Paul Trayhurn, for two years, to continue the studies on the breakdown of protein in the human lens. It was found that the properties of the proteinase in the human lens were apparently identical to those of the enzyme in the bovine lens. The properties of the enzyme were examined in some detail.

Structural studies of gamma crystallin in the lens

Miss (now Dr.) Slingsby submitted her thesis on this subject in 1973. The main component of bovine gamma crystallin was studied in great detail and a complete covalent structure was proposed. Dr. Slingsby is now using her chemical experience of lens proteins in a collaborative study of their X-ray crystallography and three dimensional structure at Birbeck College, University of London.

RNIB GRANTS FOR RESEARCH INTO THE PREVENTION OF BLINDNESS 1973-1979

Bath Eye Infirmary

1976 Myopia £ 500

Birmingham and Midland Eye Hospital

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City University, London

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University of Bristol, Bristol Eye Hospital

1976 Immunotherapy in herpes simplex & keratitis £ 4,783

* University College Hospital Medical School, London

1974-9 Diabetic retinopathy £30,000

University of East Anglia, Norwich

1973-8 Biochemistry of senile cataract £ 1,473

University of Oxford, Nuffield Laboratory of Ophthalmology

1977 Tear Film £ 4,520

* Grant made by British Foundation for Research into Prevention of Blindness

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About the RNIB

The RNIB was founded in 1868. It is the largest organisation of its kind in the world

Its governing council includes representatives of regional associations for the blind, national and specialist organisations of blind people, other national agencies for the blind and local government

RNIB receives contributions from national and local government towards some of its services, but depends on funds from donations, covenants and legacies to continue and expand the help it can give to the 120,000 blind people in the UK

RNIB is represented on the World Council for the Welfare of the Blind.

